PIONEER IN BEHAVIORAL PHARMACOLOGY: A TRIBUTE TO JOSEPH V. BRADY JAMES E. BARRETT

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The contributions of Joseph V. Brady to behavioral pharmacology span more than 50 years and range from early studies using the Estes-Skinner (conditioned emotional response) procedure to examine drug effects and various physiological processes in experimental animals to the implementation of mobile methadone treatment services and to small group behavioral analyses in simulated space environments. This expansive range of activities is based on Brady's insight and innovative use of behavioral procedures, his spirited and unabashed enthusiasm for the discipline and its philosophical underpinnings, together with a collegiality and commitment to the experimental analysis of behavior that is both legendary and inspirational. These contributions are summarized and highlighted in this tribute that focuses primarily on Brady's contributions to behavioral pharmacology but which also acknowledges his conceptual and technical contributions spanning multiple disciplines.

Key words: J.V. Brady, behavioral pharmacology, schedules of reinforcement, conditioned emotional response, experimental analysis of behavior, neuropsychopharmacology, neuroscience, behavioral physiology

Fields of scientific endeavor arise and are sustained in multiple ways. Despite their origins, they are frequently sowed by insight and cultivated by inspiration together with a vision well beyond what to many may seem limited. Scientific endeavors are often facilitated by a combination of these qualities, coupled with a charismatic and inspiring personality that, together, provide fertile ground for scientific advances, for the training of students and the education of colleagues to help form a solid foundation for future growth. Joseph V. Brady embodies these many characteristics and qualities and stands tall as a pioneer in the field of behavioral pharmacology. This article is intended to capture many of Brady's contributions to the discipline of behavioral pharmacology and joins other such tributes to key figures who have contributed to the emergence and viability of behavioral pharmacology as well as to the experimental analysis of behavior (see Barrett, 2002, 2006; Branch, 2006; Marr, 2006: Zeiler, 2006).

Brady's contributions span a near 60-year period and continue to this day. The scope of his engagement with behavioral, physiological, neurobiological and pharmacological research is, in a literal sense, beyond earthly boundaries. It ranges from the study of the conditioned emotional response in the rat (Hunt & Brady,

1951), to early research in the area of psychopharmacology (Brady, 1956), to drug abuse and dependence (Brady & Lukas, 1984), and to efforts within the domain of the National Aeronautics and Space Administration (NASA) where he pioneered studies to examine effects of individual and group performance in closed environments simulating space travel (Brady, 1990; Brady, Kelly, & Hienz, 1999). Most recently, Brady has extended his efforts to treatment approaches to drug dependence by initiating a mobile methadone treatment service in the Baltimore community (Brady, 1993b). This breadth of activities, the unique and resolute enthusiasm and passion behind them, together with his commitment to the field and support of those entering as well as residing within his scientific sphere, approach legendary proportions. Balanced by a large dose of humor and jocular collegiality together with experience-based philosophy and wisdom, but always with an unwavering passion for the science, there is no doubt that Brady has been tremendously influential in the fields of the experimental analysis of behavior and in behavioral pharmacology. It is difficult to summarize all of his scientific contributions and personal qualities but it is hoped that this review will capture Brady's many scientific achievements, as the more personal aspects of his career are best told in his own words (see Brady, 1993a; 2008; Journal Interview, "Conversation with Joseph V. Brady," 2005).

THE CONDITIONED EMOTIONAL RESPONSE

The beginnings of Brady's research in behavior and behavioral pharmacology were largely initiated by a graduate level course at the University of Chicago that required students to select an experiment from the literature and replicate the results of that study (see Journal Interview, 2005). Brady opted to replicate the Estes and Skinner (1941) experiment on the conditioned emotional response (CER). This procedure consisted of initially training food- or water-restricted rats to press a lever that resulted in the delivery either of food or water and, when responding stabilized, superimposing an auditory stimulus, such as a tone, that terminated with the delivery of shock. After a number of such presentations of the tone-shock stimulus, the rat would cease to respond when the tone came on, a result that has been widely characterized as the development of conditioned fear or anxiety. Brady manipulated the shock intensity and obtained complete suppression of the lever pressing behavior during the preshock stimulus, along with piloerection and defecation. The next step in these experiments, conducted with Hunt, was to administer electroconvulsive shock (ECS) to the rats once they had developed the conditioned emotional response (Brady, 1951; Hunt & Brady, 1951). At the time these experiments were being conducted, there was great interest within the psychiatric community on methods of developing "experimental neuroses" and on methods of eliminating "neuroses" with such procedures as insulin-induced comas and ECS.

The first of a series of papers to examine the CER and its potential modification by ECS established responding of water-restricted rats under a variable-interval schedule of water reinforcement. A clicker was then paired with foot shock, superimposed upon the steady baseline of water-maintained responding (Hunt & Brady, 1951). This procedure resulted in the reliable reduction of responding during the clicker (Figure 1). Once responding was suppressed, the rats were administered a series of ECS treatments that subsequently eliminated the conditioned suppression of responding during the clicker that preceded shock presentation (Figure 2). It is interesting

that although the suppression of responding during the clicker was eliminated by ECS, that treatment did not appear to affect baseline responding maintained by water, indicating that the ECS was specific to the CER. Subsequently, Brady (1951) demonstrated that the conditioned suppression reappeared following the termination of the ECS treatments and that the reemergence followed a time course indicating that the effects of ECS were not permanent.

These studies initiated an extensive series of experiments that combined behavioral, neuroanatomical, physiological and pharmacological interventions that broadened the scope and focus of the initial research and which also began collaborative efforts with other scientists such as W.J.H. Nauta, R. Galambos, W.C. Stebbins, I. Geller, J.J. Boren, W. Hodos, J. Findley and M. Sidman—a steady stream of scientists all of whom have also individually left a strong and lasting impact on the field. This diversity of science brought tremendous strength to the program of research, most of which was conducted at the Walter Reed Army Institute of Research. Brady's appreciation for the use of schedules of reinforcement (Ferster and Skinner, 1957) to engender and maintain stable behavior is clear from his initial studies of the CER, which provided cumulative records of baseline behaviors and the effects of interventions such as the presentation of electric shock. This appreciation of the power of schedules to control behavior under widespread conditions also emerged in an early paper published in Science that examined behavior maintained by intracranial self-stimulation under variable-interval and fixed-ratio schedules of reinforcement (Sidman, Brady, Boren, & Conrad, 1955). The emphasis on behavioral control by schedules of reinforcement ran as a continuous thread throughout much of his subsequent work. A figure from the Science article is reproduced here in Figure 3 and shows clearly that behavior maintained by electrical brain stimulation is remarkably similar to that maintained by the presentation of food. The disposition to use the formidable toolbox of applications provided by the experimental analysis of behavior and to apply the underlying philosophy along with the techniques was a dominant theme throughout Brady's career, as we will see in subsequent sections of this article.

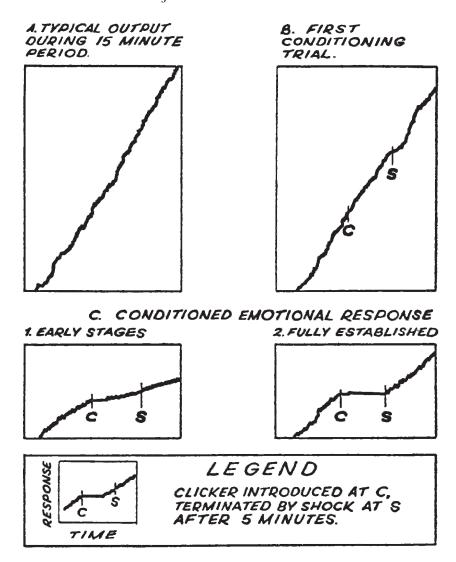


Fig. 1. Development of conditioned suppression under the conditioned emotional response (CER) procedure. In all panels, time is on the X-axis and responses on the Y-axis. The top left frame (labeled A) represents responding of a rat under the variable-interval schedule of water presentation prior to the introduction of the clicker and shock. Frame B is the first conditioning trial where the clicker (C) and shock (S) are superimposed on the water-maintained baseline. The subsequent panels represent early and late stages in the development of conditioned suppression where it can be seen that upon repeated presentations of the clicker–shock pairing, responding is almost completely suppressed during the 5-min period preceding shock delivery but recovers quickly once the shock and the clicker are terminated. Adapted from Hunt and Brady (1951).

This early focus on objective behavior and an appreciation for experimental control is evident also in the title of one of the first behavioral pharmacological papers (Brady, 1953) in which he posed the question "Does tetraethylammonium reduce fear?" A previous publication had reported that tetraethylammonium (TEA) decreased the running speed of rats in an escape—avoidance procedure and concluded that this outcome was due to a

reduction in the "drive of fear" as a result of the partial blocking of the autonomic ganglia by TEA (Auld, 1951). Brady acknowledged the need for more direct experimental control for the possible effects of TEA on locomotor behavior and conducted two experiments "designed to investigate further the alleged fear-reducing properties of TEA" (page 307). He compared the effects of TEA using two procedures—one using the CER procedure

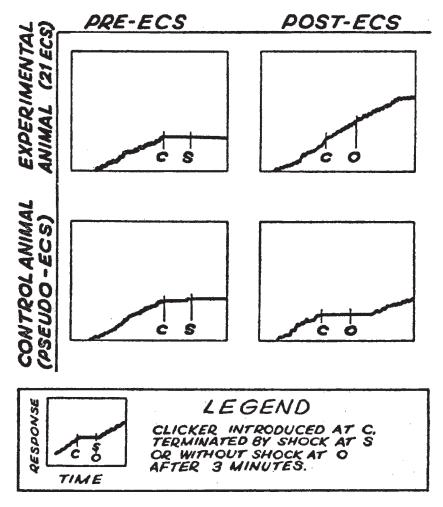


Fig. 2. Cumulative response records of rats under the procedure where electroconvulsive shock (ECS) was delivered and this resulted in an attenuation of the suppression in the presence of the clicker (top right panel); the lower right panel is taken from a pseudo-ECS subject and demonstrates that responding remained suppressed during the clicker preceding shock delivery. Recording is the same as in Figure 1A except that "O" indicates that no shock was delivered during the time when ECS was administered. Adapted from Hunt and Brady (1951).

described above to assess whether TEA would affect fear alone (i.e., behavior suppressed during the clicker preceding shock delivery) or would also affect lever pressing maintained by water. The second procedure examined TEA on behavior of food- and water-deprived rats that were studied in both a running wheel and a runway. Both food and water were available at one end of the 8-ft runway so that running speed could be assessed with an appetitive task (i.e., food- and water-maintained) and compared with the behavior maintained under the aversive CER procedure. General activity in the running wheel was also assessed. This experiment was significant

in that it demonstrated that TEA completely suppressed lever pressing maintained by food—none of the rats in the CER study made a single response. It was of some interest that 5 of the 6 rats defecated during the clicker suggesting that there was no attenuation of this response, often used as an index of emotionality. In the second portion of this study, both activity in the running wheel and the speed with which the rats traversed the runway to gain access to food and water were also markedly reduced by TEA, suggesting that the drug's effects were not specific to behavior under the control of aversive or noxious stimuli. In what was to

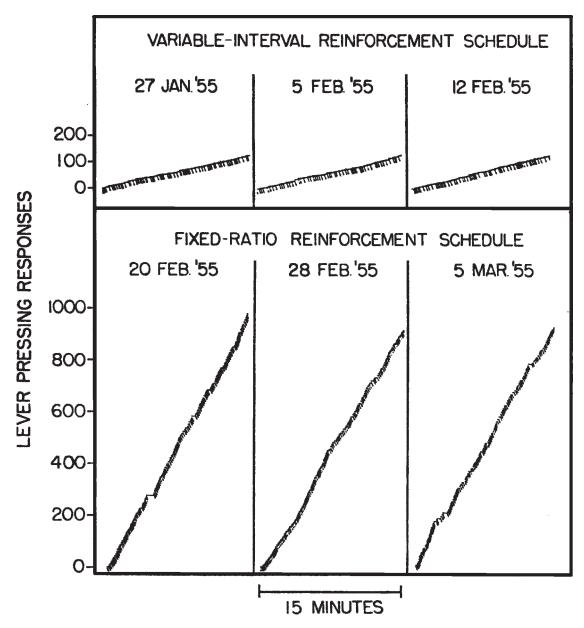


Fig. 3. Cumulative response records of lever pressing by rats under a variable interval schedule (top panels) and under a fixed ratio schedule of electrical brain stimulation. The oblique marks on the records indicate brain stimulation. Note that responding was maintained at intermediate rates under the variable interval schedule and at high rates under the fixed ratio schedule. These rates and patterns are similar to those maintained by food and also were maintained over several days at comparable levels. Adapted from Sidman et al. (1955).

become a harbinger of things to come in the discipline of behavioral pharmacology, this article concluded that "the results of these experiments raise serious questions about the validity of previously published 'fear-reduction' interpretations of TEA upon behavior" (page 310).

FURTHER ASSESSMENT OF DRUG EFFECTS ON EMOTIONAL BEHAVIOR: APPLICATIONS TO PSYCHOTHERAPEUTIC DRUGS

One distinctive characteristic and attribute of Brady's career has been his ability to foresee a need and to then blend his sophisticated background in and commitment to behavior with emerging technology to achieve a much loftier objective than could be achieved with either behavior or technology alone. There are many such illuminating and recurring themes throughout his career and it is, as mentioned earlier, astonishing how many different spheres Brady has set in motion. Such was the case where, with the advent of effective psychotherapeutic drugs in the 1950s, he saw the opportunity for behavior analyses to add significantly to the heightened need for the pharmaceutical industry to develop suitable assays with which they could evaluate drug action. One of his earliest papers on the behavioral effects of drugs using schedulecontrolled behavior was published in Science (Brady, 1956). In this experiment, he investigated the effects of amphetamine and reserpine using the CER procedure. As he stated in the introduction to the *Science* paper, "recent developments in the use of chemicotherapeutic agents for clinical psychopathology have stimulated renewed interest in ... methods for assessing behavioral changes associated with such drug administration" (p. 1033). The results of this study, conducted both with rhesus monkeys and rats, are depicted in the cumulative records in Figure 4. These records show the characteristic suppression of responding during the preshock stimulus while responding is otherwise maintained at a reasonably steady rate. Under this procedure, amphetamine increased responding under the variable- interval schedule but did not affect responding suppressed during the stimulus that terminated with shock presentation. In contrast to the results with amphetamine, reserpine decreased responding maintained under the variable-interval schedule but increased responding that was suppressed during the presentation of the stimulus preceding shock presentation. The effects were reported to be similar in both rats and monkeys and it was concluded that "the method described does provide an approach to the selective assessment of specific drug-behavior relationships in the affective sphere" (Brady, 1956, p. 1034)—a remarkably oblique and understated way of commenting that it is possible pharmacologically to separate the effects of drugs on behavior maintained by food versus those controlled by noxious stimuli such as

electric shock presentation. This theme of the effects of drugs on behavior controlled by either food or shock has recurred repeatedly throughout the intervening 50 or so years of behavioral pharmacological research (Barrett & Katz, 1981; Kelleher & Morse, 1968; Morse, McKearney, & Kelleher, 1977) and it is often overlooked that this paper by Brady was the first experimental approach to examine this question using suitable pharmacological compounds and schedule-controlled behavior.

In a follow-up publication to the results of the Science article, Brady (1991) published a "tribute" to the subject (Rat AA-26) whose cumulative records were some of the first to appear in Science and reproduced here in Figure 4, and in doing so, also commented on the effects of reserpine on punished behavior reported by Geller and Seifter (1960). The principal difference between the CER and the punishment procedure was that the shock occurred independently of responding in the CER procedure, whereas under the punishment procedure responding produced shock; both procedures employed a distinctive stimulus and both procedures resulted in a marked reduction in responding during the stimulus period. In contrast to the effects of reserpine in the CER procedure, however, where suppressed responding in the presence of the stimulus was increased by reserpine, punished responding either was not affected or was decreased by this drug. This separation of the effects of reserpine on these two forms of suppressed responding pointed quite clearly to the ability of drugs to pharmacologically differentiate behavioral effects that might otherwise appear to be quite similar. Additionally, the punishment procedure became widely employed by pharmaceutical companies in the search for anxiolytic drugs due to the finding by Geller and his colleagues that the benzodiazepines, such as chlordiazepoxide and diazepam, produced marked increases in punished behavior whereas nonanxiolytic drugs or even analgesic drugs such as morphine did not attenuate the reduction in responding under the punishment procedure (review by Pollard & Howard, 1990).

Brady clearly saw the potential for widespread application of schedule-controlled operant behavior to the pharmaceutical industry and became a very early advocate for applying these procedures to preclinical drug discovery

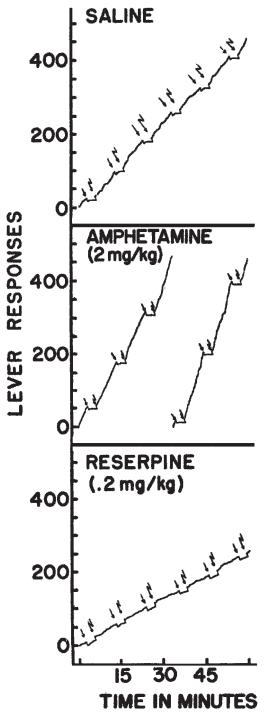


Fig. 4. Sample cumulative records for rat AA-26 depicting the effects of amphetamine and reserpine on lever pressing maintained by water and on the suppression of responding during the stimulus preceding shock delivery. The arrows indicate the onset of the preshock stimulus, when the pen deflected, and the termination of

efforts (Brady, 1958; Journal Interview, 2005). A major theoretical issue around this time was that of the effects of drugs on "emotional" behavior and whether it was possible for drugs to selectively affect behavior differentially controlled by appetitive stimuli, such as food, versus behaviors controlled by aversive stimuli such as electric shock. The issues and hypotheses involved in this controversy revolved around questions of motivation, drive reduction, and other psychological concepts that were conceptually cumbersome and experimentally intractable (see, for example, McMillan & Katz, 2002, for a review of this area of research). On a fundamental level, the issue of whether psychiatric disorders were related to aversive events that engendered anxiety and whether maladaptive behaviors ("neuroses" to use a word of the time) were similarly related, was key to establishing animal models that could provide suitable procedures for the evaluation of drugs. The issues surrounding these academic questions became somewhat less important as work with clinically effective compounds such as chlorpromazine, imipramine, chlordiazepoxide and diazepam were used to develop the first generation of animal models and evaluate the potential for identifying newer compounds that were to follow (Barrett & Witkin, in press). The important point here is that Brady saw the enormous potential for using operant conditioning procedures in this context, eschewed the more mentalistic interpretations of traditional psychology and forged ahead with his objective, experimental analyses. This vision and the research being conducted by Brady and his colleagues were instrumental in establishing the first psychopharmacology laboratory at the University of Maryland.

RELATED ENDEAVORS

In reviewing the vast and diverse contributions that Brady has made over the years since

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that stimulus at which time shock was delivered. Note that amphetamine increased responding maintained by water but not during the conditioned stimulus, whereas reserpine decreased responding maintained by water but increased suppressed responding during the period preceding shock presentation. Adapted from Brady (1956)

1951, it is possible to somewhat arbitrarily divide his scientific efforts into two main time periods, each of which is associated with a dominant theme. The first period roughly spans from 1951 to 1975, during which time he focused on the CER procedure to examine drug effects, as described above, but also to pursue other areas of research that included the study of 17-hydroxycorticosteroid changes related to the CER and to reserpine effects (Mason & Brady, 1956), cardiovascular and blood pressure regulation (Anderson & Brady, 1971), operant (instrumental) conditioning of autonomic function (Harris, Findley, & Brady, 1971; Harris, Gilliam, & Brady, 1974), and many areas that touched on psychosomatic medicine. It was also during this period that Brady published his paper in Scientific American on "Ulcers in 'executive' monkeys" (Brady, 1958) in which he demonstrated the development of gastrointestinal lesions in monkeys that could respond to avoid electric shock presentation; monkeys receiving the same number and pattern of shocks, but irrespective of their responses, did not develop ulcers. Thus, it was speculated that the ability to control the occurrence of shock was influential in contributing to the pathophysiology of ulcer

There is no clear demarcation in these diverse activities; one area of research appears to blend rather seamlessly into another in a continuous thread, strengthened by its many fibers consisting of research programs, students, colleagues and collaborators, and always—an emphasis on principles of behavior analysis. However, a second major theme to Brady's research was to emerge towards the mid-1970s, that of a focus on drug abuse, and this effort continues to this day. Characteristically, there were signs of this direction possibly as early as 1961 with a publication in *Science* on "jugular self-infusion in the rhesus monkey" (Clark, Schuster, & Brady, 1961), work that was conducted at the University of Maryland prior to Brady's move to Johns Hopkins University and the Behavioral Biology Research Center. Although, somewhat ironically, this initial paper used saline as the maintaining event, it was primarily a technical paper that helped to set the stage for much of the research that was to follow from the Johns Hopkins laboratory as well as many other laboratories that explored the maintenance of behavior by intravenous

drug administration. These efforts in the drug abuse field continue to the present and warrant a more detailed review.

DRUG ABUSE

A sizeable portion of the drug abuse research activities conducted by Brady and his colleagues at Johns Hopkins focused on the reinforcing and discriminative stimulus effects of drugs with a more general concentration on that of abuse liability and abuse liability assessment (e.g., Brady, Griffiths, Heinz, Ator, Lukas, & Lamb, 1987; Brady, Heinz, & Ator, 1990). The Division of Behavioral Biology that Brady founded combined basic research using a variety of animal species with human behavioral pharmacology and was, without question, one of the most expansive and encompassing behavioral pharmacology research enterprises to emerge. This research, conducted with many colleagues such as Nancy Ator, George Bigelow, Roland Griffiths, and Maxine Stitzer, to name just a few, embarked on numerous studies directed towards assessing abuse liability, dependence potential, and subjective effects of multiple drugs in both nonhuman primates and in humans. A distinctive feature of the program at Johns Hopkins was the use of baboons as experimental subjects. Research during this time with Bob Hienz also explored the effects of drugs on sensory processes such as auditory and visual thresholds, using these behavioral measures and psychophysical assessments to complement the behavioral data as indices of potential toxicity (Hienz & Brady, 1981). The detailed examination of the correspondence between nonhuman primates and humans in their tendency to self-administer drugs was directed towards deriving a perspective on the "relative reinforcing strength" of abused drugs, that is, arriving at a means of scaling drugs in a hierarchical arrangement with regard to their potential for abuse. These assessments relied primarily on two methods to arrive at this determination—the *progressive* ratio schedule and a drug substitution procedure. The progressive ratio schedule is one in which the number of responses required to produce a reinforcer increases in some systematic manner—for example, by doubling, or according to some other progression. The initial response requirement may be 50 and then following the delivery of the reinforcer, the ratio requirement may increase to 100 and so on. The fundamental idea behind the use of this schedule is to determine a break point for the particular drug: the point at which the behavioral requirement is too high to maintain continued responding. Theoretically, the more reinforcing the drug is, the higher the break point would be. Investigations of this measure involved the comparison of different psychomotor stimulants and barbiturates and could as well be used to compare different types of reinforcers (Brady et al., 1987).

The drug substitution procedure also has been used widely to determine the potential reinforcing value of a compound. In this procedure, responding is maintained by the administration (typically intravenous) of one drug, for example cocaine, and periodically a test compound is substituted for the maintaining drug. If the compound continues to maintain responding, it is believed also to demonstrate reinforcing effects and, therefore, likely to have some abuse potential. There are multiple complexities to this procedure that required systematic evaluation such as the duration of the substitution (i.e., one session or a series of sessions), the pharmacological similarities of the substituted drug to those of the maintaining drug in terms of rate of onset, exposure, and class, dose-substitution relationships, as well as the discriminative stimulus effects of both the drug maintaining responding and the substituted drug. The latter issue bears on the distinction between the discriminative stimulus and reinforcing effects of drugs and on a determination of whether these concepts can be differentiated experimentally with regard to abuse liability. Extensive use has been made of the drug discrimination procedure in Brady's laboratory (e.g., Brady, et al., 1990). Essentially, and in its most rudimentary form, this is a procedure in which there is an initial period of training to permit a drug to serve as a discriminative stimulus. The training consists of providing reinforcement for one response after the administration of a drug and reinforcing a different response following the administration of saline. The two responses may be those of responding on the left lever of a two-lever panel following drug administration and on the right lever following saline administration. After a number of training sessions, the drug

or saline administration serves as a discriminative stimulus that controls responding much the same way other discriminative stimuli do; responding in the presence of either drug or saline is differentially reinforced. Other doses of the training drug, or other drugs can be substituted, much the same way this substitution occurs in the drug self-administration procedure. When a test drug substitutes for the training drug in the drug discrimination procedure, it is believed to share similar discriminative effects to the training drug and, because the stimuli in this case are interoceptive rather than external to the organism, it is said occasionally that the substitution of a drug shares similar subjective effects to the training drug. Moreover, if the training drug is abused, drugs that substitute are often also believed to share similar abuse liability. Taken together, the drug self-administration and the drug discrimination procedures were employed with the view that there was utility for these procedures to classify or screen drugs for their risk for abuse. The juxtaposition of these procedures has prompted many questions of an experimental and theoretical nature. One such question was whether the reinforcing and discriminative characteristics of a drug reflect identical processes with regard to the implications for drug abuse liability, or whether it is possible to separate these two assessments. For example, is it possible that a drug will share similar discriminative stimulus effects with an abused drug (i.e., will substitute) but yet will not maintain responding in the self-administration procedure? Answers to these types of questions remain at the forefront of this area of research and are likely to be pursued and answered by the types of behavioral paradigms established and thoroughly researched by the types of procedures so extensively employed by Brady and his colleagues.

There has also been a treatment component to these basic research activities as Brady explored the utility and implementation of a mobile methadone maintenance treatment approach in the Baltimore area (Brady, 1993b; Greenfield, Brady, Besteman, K., & De Smet, 1996). Characteristically, there was a pragmatic aspect—provide more easily accessible services to an underserved group in need of treatment and retention in a methadone program—and an experimental aspect that

was designed to collect data on efficacy, retention, outcome and patient characteristics. The data collected from these initiatives clearly suggested that, compared to the fixed-site programs in Baltimore, the mobile methadone health service provided greater accessibility, but importantly, longer retention in the program. Previous work had established that longer retention times were related to fewer arrests, less frequent cocaine use, and higher family income. Thus, the significantly higher probability of remaining in treatment under the mobile methadone maintenance treatment program appears not only to be a useful means of providing services but also is likely to result in a lower incidence of crime and further substance abuse, as well as in gainful employment.

CONCLUSIONS

The intent of this article has been to provide a panoramic perspective on Joe Brady's many contributions to the field of behavioral pharmacology and to touch briefly on the many other dimensions of his extraordinarily productive career. Brady's presence early on in the field of behavioral pharmacology undoubtedly has had a profound influence on the emergence and distinctive characteristics of the discipline and on the individuals that populate the field which now has many forms and reaches into many other areas of neuroscience and neuropsychopharmacology. In his more recent writings, Brady talks about being the beneficiary of a "fortuitous environment" as one way of accounting for his career and for his many contributions to behavioral pharmacology (Brady, 2008, p 29). Without question, the environment has shaped Brady's behavior and provided abundant opportunities for him to explore and exploit the behavioral space in which he worked and which helped to provide direction to the emergence and evolution of behavioral pharmacology and the many other related disciplines touched upon in this article. However, as is well known, the interaction between an individual and that individual's environment is dynamic. The environmental consequences that follow behavior alter subsequent behavior and behavioral activities can modify the environment. Just as organisms are affected by their environment, they too have an *effect* on the environment. Joe Brady

may be a product of his environment, as are we all, but he has also profoundly modified his environment and that of others by virtue of his unremitting commitment to behavioral analysis, to the study of drugs, and to the training, support, education and appreciation of countless students and colleagues.

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